UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/523,454	03/22/2005	Augustinus Bader	LORWER P33AUS	7961

20210 7590 08/08/2006

DAVIS & BUJOLD, P.L.L.C.
112 PLEASANT STREET
CONCORD, NH 03301

EXAMINER	
FORD, ALLISON M	

ART UNIT	PAPER NUMBER
1651	

DATE MAILED: 08/08/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/523,454	BADER, AUGUSTINUS	
	Examiner	Art Unit	
	Allison M. Ford	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 June 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *61-86* is/are pending in the application.

4a) Of the above claim(s) *74-86* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *61-74* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants' response of 15 June 2006 has been received and entered into the case. Claims 1-60 are cancelled. New claims 61-86 have been entered, with claims 74-86 being withdrawn from consideration as being directed to non-elected subject matter. Claims 61-73 have been considered on the merits, as far as they read on the elected species: "hydrogel" as the boundary layer material; and "lipid layer" as the intermediate layer material.

Claim Objections

In claim 63, it appears it would be more appropriate to claim, "The method according to claim 61, wherein the inert material used to form the porous support structure is phosphate."

In claim 64, it appears it would be more appropriate to claim, "The method according to claim 61, wherein the cell-impermeable boundary layer material is a biological material or a synthetic material."

In claim 65, it appears it would be more appropriate to claim, "The method of claim 64, wherein the cell-impermeable boundary layer material is a hydrogel."

In claim 66, it appears it would be more appropriate to claim, "The method of claim 61, wherein the cell-impermeable boundary layer material is gas-permeable."

In claim 69, it appears it would be more appropriate to claim, "The method of claim 68, wherein the intermediate layer is a lipid layer (elected species)."

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 61-73 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Initially it is noted that claims 61 and 70 are quite verbose in that their use of alternative language complicates and confuses the claim language, for example "forming one of an implant and a prosthesis" or "at least one of shaping and sizing" or "at least one of nutrients and oxygen."

With regards to the phrase, "one of an implant and a prosthesis," one of ordinary skill in the art would consider "implant" and "prosthesis" to be equivalents in the context of the instant application; therefore the examiner does not believe it is necessary to use these terms in the alternative, but rather suggests the term "implantable tissue construct" to clearly convey that the final product comprises a composite scaffold material and living cells which is intended to replicate, augment and/or replace tissue/organ function upon implantation *in vivo*.

With regards to the phrase, "at least one of shaping and sizing," it is not clear if the step of a) *forming* the material into a porous structure is to comprise either or both of shaping and sizing, (e.g. "forming the material into a porous structure *by* shaping and/or sizing the porous support structure") or if the actions *forming* is to be in addition to at least one of shaping and sizing. Furthermore, it is noted that forming, shaping and sizing involve considerable overlap, for in 'shaping' a mass, one is also 'sizing' the mass, and vice versa, and both actions are considered means of 'forming' the mass; therefore, requiring the actions of 'forming', 'shaping' and 'sizing' as alternatives does not appear to be necessary, but rather makes the claim language confusing.

With regards to the phrase, "at least one of nutrients and oxygen" it is not clear if applicants intended for the claim to only require one of these, as one of ordinary skill in the art will recognize that both oxygen and nutrient supply is necessary for mammalian cell growth. It is noted that the claim is not limited to mammalian cells, or even eukaryotic cells, and as such can encompass culture of anaerobic bacterial cells on the porous support structure; however, it appears from the context of the application that

the 'living cells' are to be aerobic mammalian cells in order to replicate natural human tissue, in such case it would be required that *both* oxygen and nutrients be provided to the cells in order to successfully produce the desired tissue replacement.

Furthermore, in claims 61 and 70, the first recited step ("forming a material...") the term "corresponding to a shape and size of a human body part to be replaced..." renders the claims indefinite, as the size and shape of the implant/prosthesis is defined only in reference to an object which is variable (the size and shape of a human body part). The size and shape of human body parts differ based on a variety of factors, including the size, age, health, etc of the individual. The board has held that defining an object in reference to an object which is variable, in this case the size and shape of a human body part, does render the claim indefinite. See *Ex parte Brummer*, 12 USPQ2d 1653 (Bd. Pat. App. & Inter. 1989).

Still further, in the fifth recited step of claim 61 and the sixth recited step of claim 70 ("following formation of one of the implant and the prosthesis, removing the boundary layer and thereby resulting in one of the implant and the prosthesis formed...") it is not clear what applicant is considering the final product: the implant/prosthesis complete with the boundary layer (e.g., "*following formation* of the implant/prosthesis...) or if the final product is produced after the boundary layer is removed (e.g., "removing the boundary layer and *thereby resulting in* the implant/prosthesis...).

In order to provide clarity, the following is suggested for claim 61:

A method of forming an implantable tissue construct for replacement for a human body part, comprising:

a) forming an inert material into a porous support structure having a shape and size corresponding to the shape and size of the human body part to be replaced;

b) applying a boundary layer of cell-impermeable material to the porous support structure;

c) introducing living cells into the porous structure;

d) promoting cell growth by introducing nutrients and oxygen to the living cells; then

e) removing the boundary layer; thereby producing an implantable tissue construct which corresponds to the shape and size of the human body part to be replaced.

The following is suggested for claim 70:

A method of forming an implantable tissue construct for replacement for a human body part, comprising:

a) forming an inert material into a porous support structure having a shape and size corresponding to the shape and size of the human body part to be replaced;

b) applying a boundary layer of cell-impermeable material to the exterior of the porous support structure;

c) providing the porous support structure with at least one inlet;

d) introducing living cells into the porous structure;

e) promoting cell growth within the porous support structure by introducing nutrients and oxygen to the living cells, so that the cells conform to the size and shape of the porous support structure; then

f) removing the boundary layer; thereby producing an implantable tissue construct which corresponds to the shape and size of the human body part to be replaced.

Additionally, in claim 62, it is unclear how the porous support structure is formed so that it is either removable or convertible by the cells; it is unclear what positive method step is required to form the porous support structure in such a way. Rather, it appears the claim should limit the material of the porous support structure.

Similarly, in claims 71 and 72, it is unclear how the boundary layer is formed so that it is mechanically removable from, detachable from or soluble from the porous support structure, or how it is formed so that it is vascularized or prevascularized; it is unclear what positive method step is required to

form the boundary layer so that it is comprises these properties. Rather, it appears the claim should limit the material of the boundary layer to one which imparts these characteristics. Furthermore, it remains unclear what 'prevascularized' comprises.

In claim 73, it remains unclear at what point during the method of claim 61 the plurality of porous support structures are introduced into a nutrient solution (e.g., before application of boundary layer, after application of boundary layer, etc).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 61-64, 66, 68 and 70-72 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bader (WO 01/09282) (translation provided for US national stage application 10/048,440 replied upon for English version- pages cited are those of application 10/048,440).

Bader teaches a cell culturing device and a method of culturing cells on said device to produce a tissue construct which can be in a desired shape (which applicant calls forming an implantable prosthesis). The cell culture device of Bader comprises a support, such as a cell carrier plate; a carrier film laid directly on the support; and a flexible plastic cell-culture film that is attached at the edges to the carrier plate and/or carrier film so as to form a cell culture chamber between the two films (See Bader, abstract). The cells may be cultured directly in the cell culture chamber on the films or an extracellular matrix may be placed in the interior of the cell culture chamber to provide a substrate for the cells (See Bader, Pg. 11, ln 7-19).

In comparing the method of Bader (WO 01/09282) to the instant invention, the extracellular matrix is considered to read on the 'porous support structure'; the films are considered to read on the 'boundary layer' which surrounds the extracellular matrix (porous support structure). The extracellular matrix (porous support structure) can comprise collagen (See Bader, Pg. 14, ln 26-36) or tricalcium phosphate (See Bader, Pg. 11, ln 14-19), both are porous materials which are permeable to the cells and can be degraded or absorbed by the cells (which applicant calls being convertible by the cells). The cell carrier and/or cell culture films (boundary layer) may be gas-permeable (See Bader, abstract); furthermore because the films form the cell culture chamber, both films (boundary layer) must be impermeable to cells so as to retain the cell culture in the defined area. The films (boundary layers) may consist of PTFE, silicone, polylactide, polyhydroxyalkanoate, or polyhydroxidebutyrates (See Bader, Pg. 18, ln 24-30); such materials are synthetically made from biological materials, thus they are considered both 'synthetic' and 'biological' materials.

The method of cell culture disclosed by Bader (WO 01/09282) comprises introducing cells into the extracellular matrix (porous support structure) which is located within the cell culture chamber formed by the films (boundary layers), and supplying nutrients to the cells on the extracellular matrix (porous support structure) via inflow and outflow lines; oxygen is supplied to the growing cells through the gas-permeable films (boundary layers) (See Bader, Pg. 16, ln 25-37 & Pg. 5, ln 13-27).

In order to more clearly show how the method of Bader reads on the instantly claimed method, each of the claimed steps will be further discussed below:

Regarding the step of forming the inert porous support material into the desired shape, it is noted that Bader teaches the extracellular matrix (porous support structure) can approximate the size and shape of a desired tissue, for example, bone, heart valve or bladder, so that the finished cell culture may be used

to reconstruct the desired tissue (See Bader, Pg. 14, ln 9-17); thus it is inherently required that an initial step comprise forming the extracellular matrix material into the desired shape and size.

Regarding the step of applying the boundary layer to the porous support structure, it is noted that Bader teaches the cells are introduced into the extracellular matrix (porous support structure) inside the cell culture chamber (which is formed by the films (boundary layers)); therefore, the extracellular matrix is placed within the cell culture chamber formed by the films (boundary layer) prior to introduction of the cells (which applicant calls applying a boundary layer of material to the porous support structure).

Regarding the step of providing the porous support structure with at least one inlet and introducing the cells to the porous support structure, it is noted that Bader teach inoculating the cells onto the extracellular matrix (porous support material) via inflow and outflow lines (which applicants call inlets) (See Bader, Pg. 16, ln 25-37 & Pg. 5, ln 13-27).

Regarding the step of promoting cell growth by introducing oxygen and nutrients into the porous structure and allowing cells to consume the nutrients and the oxygen and to grow and conform to the shape and size of the porous support structure, it is noted that Bader teach nutrients is supplied to the cells on the extracellular matrix (porous support structure) via the inflow and outflow lines and oxygen is supplied to the growing cells through the gas-permeable films (boundary layers) (See Bader, Pg. 16, ln 25-37 & Pg. 5, ln 13-27). Supply of oxygen and nutrients is considered to read on "allowing the living cells to consume the nutrients and the oxygen and to grow and conform to the shape and size of the porous support structure," especially in the absence of any evidence the method of the instant invention requires a different action. Furthermore, it is noted that the nutrient medium is considered to read on the 'intermediate layer', and thus supplying the nutrient media via the inflow and outflow lines is considered to read on the step of supplying an intermediate layer.

Finally, regarding the step of removing the boundary layers, it is noted that Bader teaches the films (boundary layers) are removable, or may be dissolvable, after the cell culture is complete (See

Bader, Pg. 14, ln 14-21). It would have been obvious to one of ordinary skill in the art to remove the films (boundary layers) after the cell culture is complete in order to recover and use the tissue construct produced, which has the shape originally provided by the extracellular matrix (porous support structure). One would expect success in removing the films (boundary layer) in order to recover the tissue construct because Bader teaches the films (boundary layer) is removable or dissolvable (Claims 61-64, 66, 68, 70-72). Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Response to Arguments

Applicant's arguments received 15 June 2006 have been fully considered. Cancellation of claims 31-60 (previously pending) have rendered the rejection of these claims moot; however, new claims 61-73 are directed to essentially the same subject matter, and thus the rejection over Bader (WO 01/09282) has been applied to the new claims, as appropriate.

Regarding the rejections under 35 USC 112, second paragraph, indefiniteness, applicants stated the new claims have amended the issues previously noted as being causes of confusion or indefiniteness; however, the new claims do present problems under 35 USC 112, second paragraph, which have been presented above.

Regarding the rejections under 35 USC 102(b) and 102(e), applicants amendments to the claims have obviated the rejections over Kleinman (Current Protocols in Cell Biology, 1998) and over Schinstine et al ('747). Specifically, the amended claims now require the porous support structure to be formed into the shape and size of a human body part to be replaced, and further require, at the conclusion, the boundary layer to be removed; neither Kleinman nor Schinstine teach or suggest these steps. Kleinman merely teaches culturing cells on a Matrigel coated substrate; the cell culture is not taught or suggested to be used as implantable tissue.construct, Matrigel (considered to be the support structure) is not formed

into the size or shape of a human body part to be replaced, and the substrate is not removed (or removable) at the end of cell culture. Schinstine, while they do teach use of the microspheres for use in an artificial liver system, each individual microsphere is not in the size or shape of a human body part, rather a multitude of the microspheres are placed into a container which replicates the size and shape of a human body part; furthermore, the sphere coating (considered to be the boundary layer) is not removable from the support structure or cells after cell culturing, but is required for use in the bioartificial liver system.

However, the rejection under 35 USC 102(b) over Bader (WO 01/09282), as presented above, stands, the arguments of applicant were not found persuasive. Specifically applicants argue that the cell culturing device of Bader does not anticipate the current cell culture system, as the device of Bader (WO 01/09282) requires cells to be cultured between a carrier film 3 and the culture film 2, wherein the culture film 2 is specifically designed to be elastic to allow the cell layer to grow while still being maintained within the cell culture area. Applicants argue that in view of the elastic culture film 2, Bader (WO 01/09282) does not teach, suggest, or disclose shaping a material, inert to living cells, into a porous support structure having a shape and a size corresponding to a shape and size of a human body part to be replaced and forming the implantable tissue construct as claimed.

It appears applicant is relying on one embodiment of Bader (WO 01/09282), wherein cells are injected directly into the cell culture chamber, and allowed to expand exponentially to produce large quantities of cell culture; however, this embodiment is not relied upon for the instant rejection, rather the rejection is based on the embodiment discussed above, wherein an extracellular matrix in the shape of a human body part (i.e. bone, heart valve or bladder (See Bader, Pg. 14, ln 9-17)), is placed within the cell culture chamber, and is used to form a tissue construct in substantially the same shape as the extracellular matrix. Therefore, the rejection of record stands.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Allison M. Ford whose telephone number is 571-272-2936. The examiner can normally be reached on 7:30-5 M-Th, alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Allison M Ford
Examiner
Art Unit 1651

LEON B. LANKFORD, JR.
PRIMARY EXAMINER